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Efficacy of once-daily tiotropium Respimat in adults with asthma at GINA Steps 2–5

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ABSTRACT

Tiotropium Respimat is an efficacious add-on to maintenance treatment in patients with symptomatic asthma. Currently, the Global Initiative for Asthma (GINA) strategy recommends tiotropium for patients at Steps 4–5. To assess the clinical benefits of tiotropium Respimat across asthma severities, GINA Steps 2–5, a *post hoc* analysis of five double-blind trials (12–48-weeks; patients aged 18–75 years) investigated the effect of tiotropium Respimat, 5 μg or 2.5 μg, versus placebo, on peak forced expiratory volume in 1 s (FEV_1) within 3 h post-dose ($FEV_{1(0–3h)}$) response, and Asthma Control Questionnaire-7 (ACQ-7) responder rate. GINA step grouping was based on patients' background treatment regimen. Baseline characteristics of patients (N = 2926) were balanced between treatments. Tiotropium Respimat showed consistent improvements in lung function across GINA steps; placebo-corrected peak $FEV_{1(0–3h)}$ improvements after tiotropium Respimat 5 μg and 2.5 μg were: Step 2 (Week 8), 135 mL (95% confidence interval: 84, 187) and 155 mL (103, 206); Step 3 (Week 24), 187 mL (139, 235) and 235 mL (187, 283); Step 4 (Week 24), 111 mL (63, 159) and 181 mL (35, 326); Step 5 (Week 24; 5 μg only), 164 mL (5, 323). Asthma control improved with tiotropium Respimat versus placebo, showing statistical significance (nominal *P* value) with tiotropium Respimat 5 μg at Step 4 (odds ratio 1.36 [1.03, 1.78]). Safety profiles were similar between treatments. In conclusion, tiotropium Respimat add-on therapy improves lung function, and may improve asthma control, in adults across disease severities.

Plain language summary

Tiotropium is an inhaled drug used to treat severe asthma. Yet people with mild asthma can also suffer from symptoms if their condition is not well managed. So here we ask: can add-on tiotropium also benefit people with milder asthma?

Many large studies have tested tiotropium added on to different asthma treatments. Here, we brought together data from nearly 3000 patients. We grouped them by how severe their asthma was. We used a global measure of asthma severity (GINA Steps). We looked at how helpful add-on tiotropium was at managing asthma.

In these large studies, add-on tiotropium improves how well people's lungs work in patients with mild, moderate or severe asthma. There were also signs that people had better control of their symptoms, although further studies are needed to confirm this.

Overall, add-on tiotropium could be a useful treatment option for people living with mild, moderate or severe asthma.

1. Introduction

Lack of asthma control is found in patients across a wide range of severities [1]. Despite currently available therapies and detailed guidelines, between 40 and 55% of patients with asthma remain symptomatic [2–4]. While clinicians need to ensure adequate treatment

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Abbreviations

ACQ	Asthma Control Questionnaire
AE	adverse event
COPD	chronic obstructive pulmonary disease
FEV_1	forced expiratory volume in 1 s
$FEV_{1(0–3h)}$	forced expiratory volume in 1 s within 3 h post-dose
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroids
IgE	immunoglobulin E
LABA	long-acting β_2-agonist
LAMA	long-acting muscarinic antagonist
LTRA	leukotriene receptor antagonist
OCS	oral corticosteroids

adherence, correct inhaler technique, and treatment of comorbidities, there is often still a need for additional management strategies, such as a written asthma action plan and consideration of options to intensify treatment with add-on therapies at each step as required (Fig. 1) [5].

Tiotropium is one such add-on option and is the most extensively studied long-acting muscarinic antagonist (LAMA) and the only one approved for use in asthma; it produces a bronchodilatory effect through a different mechanism to other maintenance bronchodilator therapies in asthma, specifically long-acting β_2-agonists (LABAs) [6,7]. By binding to muscarinic acetylcholine receptors in the lungs, LAMAs reduce the bronchoconstriction effect of acetylcholine, leading to a reduction in smooth muscle tone and contraction as well as airway obstruction caused by mucus secretion [8].

In the Global Initiative for Asthma (GINA) strategy, tiotropium is currently recommended for use in patients at GINA Steps 4 and 5 who are older than 12 years [5]. Tiotropium is currently approved as an add-on to inhaled corticosteroids (ICS)/LABA combinations in patients with asthma in several countries. In the US, tiotropium 2.5 μg is approved for the long-term, once-daily, maintenance treatment of asthma in patients aged 6 years and older [9]. In the EU, the indication is for tiotropium 5 μg and has recently been updated for use as an add-on maintenance bronchodilator treatment in patients aged ≥6 years with severe asthma who experienced one or more severe asthma exacerbations in the past year [10]. In the tiotropium clinical trial program in adults with asthma, the efficacy and safety of tiotropium was assessed using the Respimat Soft Mist Inhaler device. This device has been optimized to ensure a consistent drug delivery, penetrating deep into the patients' lungs, with a reduced need for patient coordination or inspiratory effort [11]. Clinical trials have shown that tiotropium Respimat is well tolerated and efficacious as add-on therapy to maintenance ICS with and without additional controllers in adults with symptomatic asthma [12–20].

The current *post hoc* analysis explored whether patients from a range of asthma severities, classified using the GINA steps, will benefit from tiotropium Respimat compared with placebo added to maintenance therapy in terms of improvements in lung function and asthma control.

2. Methods

2.1. Study design and treatment

Efficacy data were pooled from five Phase III, double-blind, placebo-controlled trials of 12- to 48-week duration: the GraziaTinA-asthma

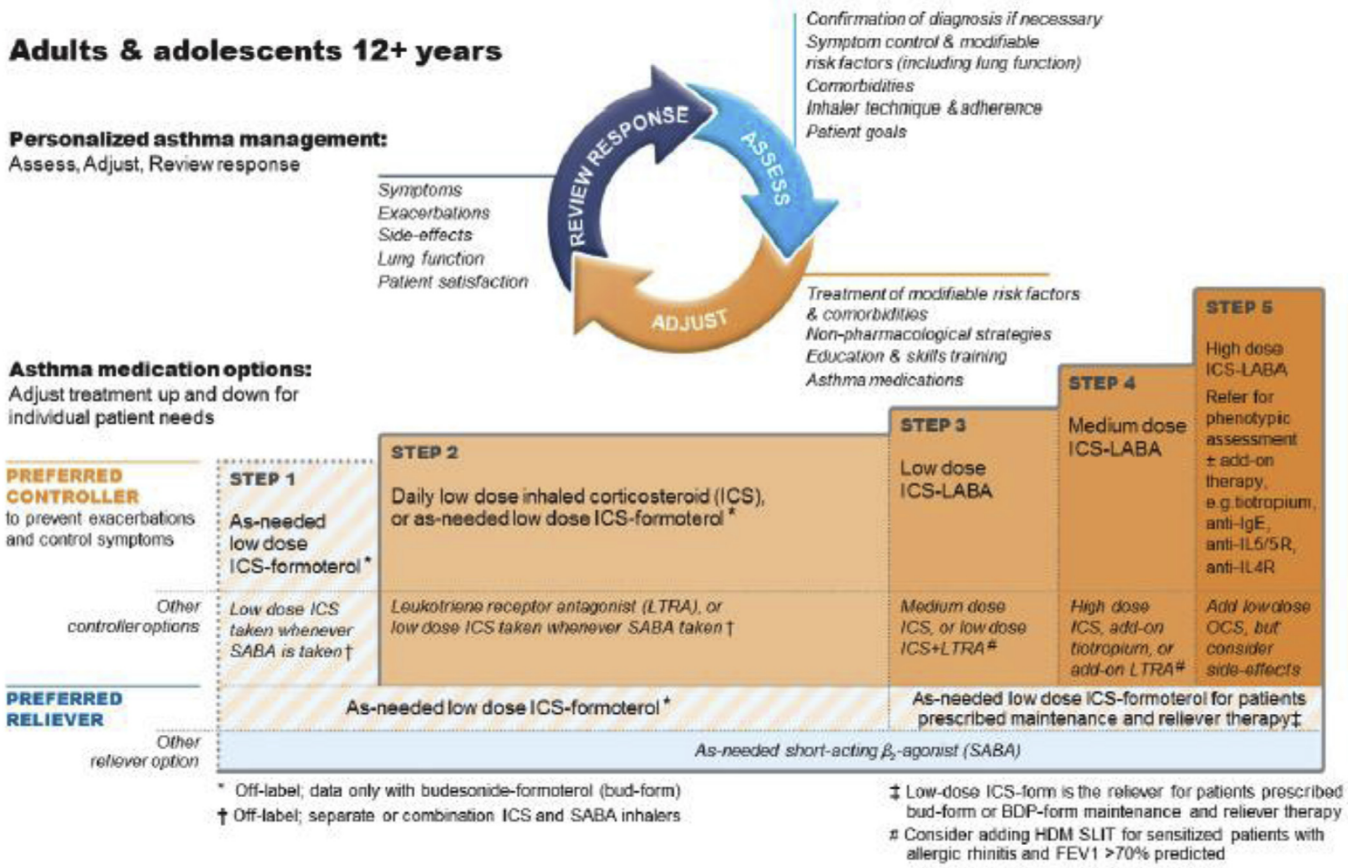

Fig. 1. The 2019 GINA asthma treatment strategy [5]: ©2019 Global Initiative for Asthma, available from www.ginasthma.org, reprinted with permission.

trial (symptomatic mild asthma) [19], MezzoTinA-asthma replicate trials (symptomatic moderate asthma) [15] and PrimoTinA-asthma replicate trials (symptomatic severe asthma) [17]. An overview of these trials is summarized in Table 1.

Salmeterol 50 μg twice-daily was a treatment arm only in MezzoTinA-asthma. Therefore, inclusion of these patients did not conform with the overall purpose of this analysis since it did not allow for assessment across GINA step severities. In this *post hoc* analysis, patients were categorized into groups based on their baseline treatment regimen, according to the GINA stepwise approach. Briefly, Step 2 patients were receiving ICS ≤400 μg budesonide/equivalent; Step 3 patients were receiving either ICS ≤400 μg budesonide/equivalent and either a LABA or LTRA as an additional controller, or ICS > 400 μg budesonide/equivalent alone; Step 4 patients were receiving ICS > 400 μg budesonide/equivalent and either a LABA or LTRA as an additional controller; and Step 5 patients were receiving ICS > 400 μg budesonide/equivalent and a LABA, plus either OCS or anti-IgE treatment.

Endpoints evaluated in this analysis are peak forced expiratory volume in 1 s (FEV_1) within 3 h post-dose ($FEV_{1(0–3h)}$) response and trough FEV_1 (pre-dose) response in patients stratified according to GINA Steps 2–5. These endpoints were compared at Week 24 for Steps 3–5; for Step 2 these were compared at Week 8 when a common visit was shared between the GraziaTinA-asthma and MezzoTinA-asthma trials. Asthma Control Questionnaire (ACQ-7) data were analyzed by examining responder rates, with a responder defined as having a minimal clinically important improvement in ACQ-7 total score of ≥0.5 units from baseline. In this analysis, this was considered in patients in GINA Steps 3–5 in MezzoTinA-asthma and PrimoTinA-asthma, where ACQ was measured at Week 24. As ACQ was not measured after the same length of treatment in GraziaTinA-asthma, Step 2 asthma control data have not been analyzed for this publication.

All patients were aged 18–75 years. Key inclusion criteria for the original studies included documented history of asthma (from medical record or confirmed with a bronchodilator reversibility test at screening), symptomatic at screening and before randomization (defined by an ACQ-7 mean score of ≥1.5), and lifelong non-smoker or ex-smoker (< 10 pack-years) with no smoking in the year before enrollment. Exclusion criteria included a diagnosis of chronic obstructive pulmonary disease (COPD) or other significant lung disease other than asthma. All original trials were carried out in accordance with the principles of the Declaration of Helsinki. The protocols were approved by the appropriate institutional review boards or independent ethics committees, and competent authority, at each study site according to national and international regulations. All patients provided written, informed consent.

2.2. Statistical analyses

In this *post hoc* analysis, all presented *P* values are nominal and analysis should be considered exploratory, i.e. there is no pre-defined hypothesis testing. For the lung function measures, within each GINA Step, peak $FEV_{1(0–3h)}$ and trough FEV_1 responses were analyzed using a restricted maximum likelihood-based mixed-effects model with repeated measures. The fixed interaction terms 'treatment', 'study', 'visit', 'baseline', 'treatment by visit', and 'baseline by visit' were included in the model, and the term 'patient' was used as a random effect. The interaction term 'treatment by trial' was added to evaluate the treatment effect across the trials. Adjusted means (with standard errors) were calculated with 95% confidence intervals (CIs).

For the asthma control analyses, within each GINA Step, ACQ responder rates were analyzed using odds ratios (tiotropium Respimat/placebo) and corresponding two-sided 95% CIs. The two-sided *P* values (calculated as 2*one-sided *P* value in the direction corresponding to testing the null hypothesis) are based on Fisher's exact test.

Table 1
Overview of the clinical trials included in the pooled analysis.

Study	Study duration	Baseline treatment	Disease severity*	Treatment	Endpoints considered in this *post hoc* analysis**		
					Peak $FEV_{1(0–3h)}$	Trough FEV_1	ACQ responder rate
GraziaTinA-asthma [19] (NCT01316380)	12 weeks	ICS 200–400 μg budesonide (or equivalent)	GINA Step 2	• Tiotropium 5 μg† • Tiotropium 2.5 μg† • Placebo†	Primary (measured at Weeks −4, 0, 4, **8**, 12, 15)	Key secondary (measured at Weeks −4, 0, 4, **8**, 12, 15)	Secondary (measured at Weeks −4, 0, 12)
MezzoTinA-asthma [15] (NCT01172808/NCT01172821)	Two 24-week replicate trials	ICS 400–800 μg budesonide (or equivalent) with or without additional controller medications	GINA Steps 2–4	• Tiotropium 5 μg† • Tiotropium 2.5 μg† • Salmeterol 50 μg‡ • Placebo§	Co-primary (measured at Weeks −4, 0, 4, **8**, 16, **24**)	Co-primary (measured at Weeks −4, 0, 4, **8**, 16, **24**)	Co-primary (measured at Weeks −4, 0, 4, 8, 16, **24**)
PrimoTinA-asthma [17] (NCT00772538/NCT00776984)	Two 48-week replicate trials	ICS ≥800 μg budesonide (or equivalent) plus a LABA with or without additional controller medications	GINA Steps 4–5	• Tiotropium 5 μg† • Placebo†	Co-primary (measured at Weeks −4, 0, 4, 8, 16, **24**, 32, 40, 48, 52)	Co-primary (measured at Weeks −4, 0, 4, 8, 16, **24**, 32, 40, 48, 52)	Secondary (measured at Weeks −4, 0, 4, 8, 16, **24**, 32, 40, 48, 52)

*Patients categorized into GINA Steps based on baseline treatment regimen. **Times when endpoints were measured are shown in brackets; bold text indicates the weeks that were pooled for this analysis; ACQ was not measured at a common visit for GraziaTinA-asthma and MezzoTinA-asthma; therefore, Step 2 asthma control data have not been pooled in this analysis. †As two puffs once daily via Respimat. ‡Delivered twice daily. Inclusion not within the purpose of this analysis. §Respimat placebo and salmeterol-matching placebo provided as part of a double-dummy design. Abbreviations: ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 s; $FEV_{1(0–3h)}$, forced expiratory volume in 1 s within 3 h post-dose; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist.

3. Results

3.1. Patients

A total of 2935 patients were treated with either tiotropium Respimat or matching placebo as add-on to low- to high-dose ICS with or without additional controllers across the five trials. Nine treated patients were not included in this analysis due to missing values for GINA classification or because they were GraziaTinA-asthma patients that were classified as Step 3 but not combined with MezzoTinA-asthma patients. In this analysis 2926 patients were included: 915 patients with Step 2 classification (612 tiotropium Respimat, 303 placebo); 1000 Step 3 (660 tiotropium Respimat, 340 placebo); 931 Step 4 (489 tiotropium Respimat, 442 placebo); and 80 Step 5 (35 tiotropium Respimat, 45 placebo). Baseline characteristics were generally well balanced across treatment groups in each trial (Table 2). Most patients were white (range: 43–83%), female (range: 57–80%), aged 40–55 years, and with a duration of asthma averaging 18–34 years (Table 2). Most trial participants had never smoked (71–87%; Table 2), and ex-smokers had a history of less than 10 pack-years and had stopped smoking at least a year before trial enrollment.

3.2. Efficacy

Significant improvements in peak $FEV_{1(0–3h)}$ and trough FEV_1 levels were observed with tiotropium Respimat 5 μg and 2.5 μg compared with placebo in patients at all asthma severities (GINA Steps 2–5; Fig. 2; Table 3). These improvements were statistically significant for all steps, with the exception of trough FEV_1 at Step 5. However, it is important to note that there were considerably fewer patients in this subgroup compared with other steps and that the mean improvement reflects the observations for the patients in Steps 2–4.

Placebo-corrected peak $FEV_{1(0–3h)}$ improvements after tiotropium Respimat 5 μg ranged from 111 mL (95% CI: 63, 159) in Step 4 patients to 187 mL (95% CI: 139, 235) in Step 3 patients (Fig. 2A). In the tiotropium Respimat 2.5 μg treatment arm, the improvements in peak $FEV_{1(0–3h)}$ versus placebo ranged from 155 mL (95% CI: 103, 206) in Step 2 patients to 235 mL (95% CI: 187, 283) in Step 3 patients (Fig. 2A).

In terms of trough FEV_1, improvements with tiotropium Respimat 5 μg versus placebo ranged from 91 mL (95% CI: 47, 136) in Step 4 patients to 131 mL (95% CI: 80, 183) in Step 3 patients (Fig. 2B). Placebo-corrected trough FEV_1 values for the tiotropium Respimat 2.5 μg treatment arm ranged from 116 mL (95% CI: 63, 170) in Step 2 patients to 180 mL (95% CI: 128, 232) in Step 3 patients (Fig. 2B).

There were consistent improvements in asthma control as measured by the ACQ-7 responder rates with tiotropium Respimat 5 μg (GINA Steps 3–5) and 2.5 μg (GINA Steps 3–4) compared with placebo, reaching statistical significance with tiotropium Respimat 5 μg at Step 4 (Fig. 3). The odds ratio for ACQ-7 response for tiotropium Respimat 5 μg versus placebo add-on at Step 4 was 1.36 (95% CI: 1.03, 1.78).

3.3. Safety

Safety and tolerability in the GraziaTinA-asthma, MezzoTinA-asthma, and PrimoTinA-asthma trials have been reported elsewhere [15,17,19,21]. The proportion of patients reporting adverse events (AEs) was similar between the add-on tiotropium Respimat treatment and placebo groups. Most AEs were mild or moderate in intensity. Dry mouth – an AE of special interest due to its association with LAMA therapy – was never classed as serious, nor did it lead to treatment discontinuation. Serious AEs and AEs leading to discontinuation were rare and similar between treatment arms. No deaths occurred.

Table 2
Overview of baseline demographic and disease characteristics across GINA Steps and treatment arms.

Demographic/characteristic	Step 2 GraziaTinA-asthma and MezzoTinA-asthma			Step 3 MezzoTinA-asthma			Step 4 MezzoTinA-asthma and PrimoTinA-asthma				Step 5 PrimoTinA-asthma	
	Tiotropium 5 μg	Tiotropium 2.5 μg	Placebo	Tiotropium 5 μg	Tiotropium 2.5 μg	Placebo	Tiotropium 5 μg	Tiotropium 2.5 μg	Placebo	Tiotropium 5 μg	Placebo
Patients, n	305	307	303	333	327	340	454	35	442	35	45
Gender, n (% male)	126 (41.3)	130 (42.3)	121 (39.9)	137 (41.1)	136 (41.6)	131 (38.5)	180 (39.6)	7 (20.0)	171 (38.7)	15 (42.9)	18 (40.0)
Race, n (%)											
White	177 (58.0)	181 (59.0)	179 (59.1)	167 (50.2)	176 (53.8)	165 (48.5)	369 (81.3)	15 (42.9)	367 (83.0)	25 (71.4)	34 (75.6)
Asian	113 (37.0)	106 (34.5)	104 (34.3)	130 (39.0)	121 (37.0)	134 (39.4)	60 (13.2)	18 (51.4)	51 (11.5)	6 (17.1)	7 (15.6)
Black/African-Am.	3 (1.0)	3 (1.0)	5 (1.7)	17 (5.1)	13 (4.0)	22 (6.5)	20 (4.4)	1 (2.9)	22 (5.0)	4 (11.4)	4 (8.9)
Am. Indian/Alaska native	12 (3.9)	16 (5.2)	15 (5.0)	19 (5.7)	16 (4.9)	18 (5.3)	4 (0.9)	1 (2.9)	1 (0.2)	0 (0)	0 (0)
Hawaiian/Pacific Isle	0 (0)	1 (0.3)	0 (0)	0 (0)	1 (0.3)	1 (0.3)	1 (0.2)	0 (0)	1 (0.2)	0 (0)	0 (0)
Age, years, mean (SD)	42.2 (12.7)	43 (13.6)	42.2 (12.8)	45.3 (12.8)	43.8 (12.5)	43 (12.8)	51.5 (12.6)	45.3 (14.5)	53 (12.7)	52.6 (12.3)	55.7 (9.2)
Smoking status, n (%)											
Never smoked	252 (82.6)	266 (86.6)	260 (85.8)	266 (79.9)	273 (83.5)	291 (85.6)	339 (74.7)	25 (71.4)	345 (78.1)	25 (71.4)	35 (77.8)
Ex-smoker	53 (17.4)	41 (13.4)	43 (14.2)	67 (20.1)	54 (16.5)	49 (14.4)	115 (25.3)	10 (28.6)	97 (21.9)	10 (28.6)	10 (22.2)
BMI, kg/m^2, mean (SD)	26.7 (5.5)	25.7 (5.2)	26.4 (5.7)	27.1 (6.1)	27.2 (6.6)	27.1 (6.2)	28.4 (6.1)	26.8 (5.8)	28.2 (6.1)	28.3 (5.3)	27.4 (6.3)
Duration of asthma, years, mean (SD)	17.8 (13.1)	18.8 (14.2)	18.0 (12.9)	23.7 (15.0)	22.9 (14.1)	21.5 (13.8)	29.3 (13.7)	22.2 (11.3)	30.2 (14.2)	29.4 (12.6)	34.3 (13.8)
FEV_1% predicted, mean (SD)	73.6 (8.1)	73.0 (8.3)	73.8 (8.2)	72.1 (8.1)	72.5 (8.4)	72.9 (8.4)	56.3 (13.0)	75.1 (8.4)	56.5 (12.4)	52.5 (12.6)	48.4 (13.7)

The baseline characteristics for 2926 patients are shown in this table. Nine patients who were treated with tiotropium or placebo were not included in this analysis; these patients had missing values for GINA classification or were GraziaTinA-asthma patients that were classified as Step 3 but not combined with MezzoTinA-asthma patients. Abbreviations: Am., American; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma; SD, standard deviation.

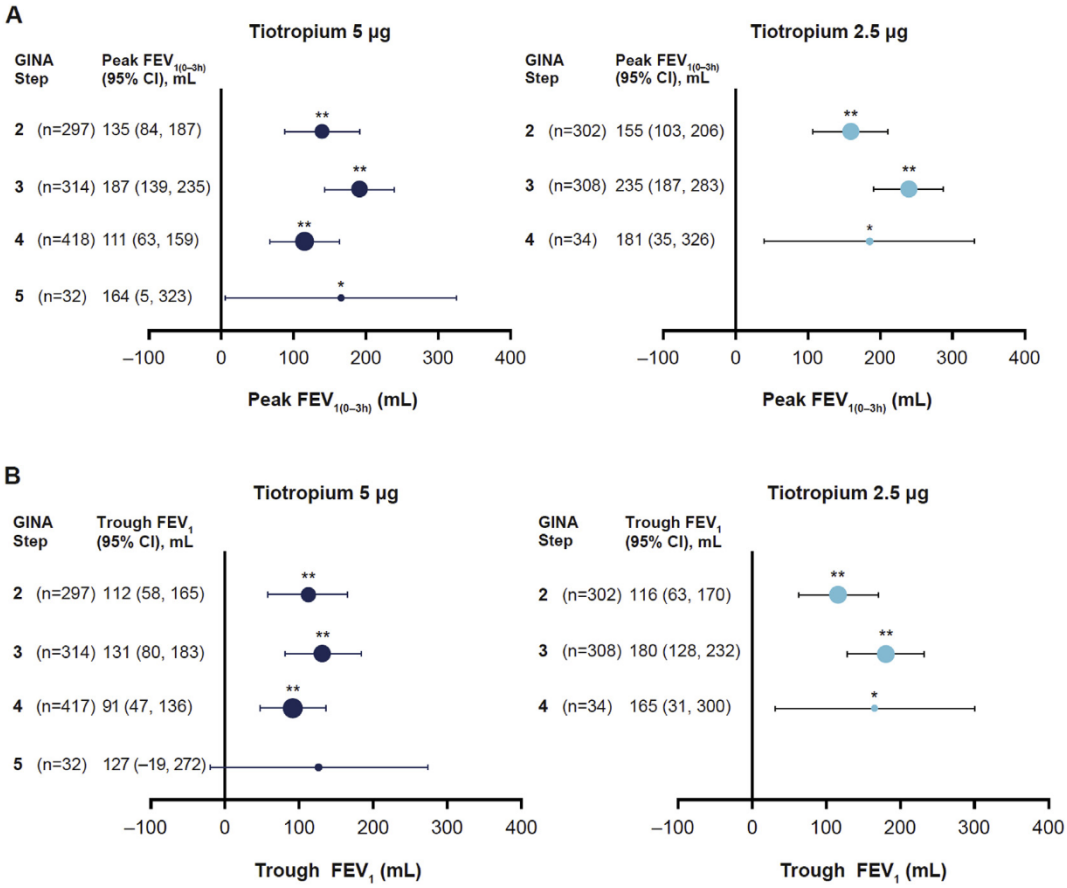

Fig. 2. Changes from baseline in (A) peak and (B) trough FEV_1 levels for tiotropium Respimat versus placebo across GINA Steps. *P < 0.05; **P < 0.0001; all vs placebo. Abbreviations: FEV_1, forced expiratory volume in 1 s; GINA, Global Initiative for Asthma. Error bars represent 95% confidence interval values. N numbers describe patients treated with tiotropium Respimat. Symbol sizes approximate patient numbers using a 7-point scale ranging from 1 to 75 to 451–525 patients.

4. Discussion

This *post hoc* analysis shows that tiotropium Respimat 5 µg and 2.5 µg add-on to maintenance therapy is effective at improving lung function compared with placebo across a range of asthma severities, classified as GINA Steps 2–5. Furthermore, compared with placebo, tiotropium Respimat 5 µg and 2.5 µg showed improvements in asthma control at Steps 3, 4, and 5.

It is interesting that, as a history of exacerbations was an entry criterion in PrimoTinA-asthma but not MezzoTinA-asthma and

Table 3
Absolute changes from baseline in peak and trough FEV_1 levels for tiotropium Respimat and placebo across GINA Steps.

Treatment	Step 2 (n = 898) GraziaTinA-asthma and MezzoTinA-asthma* Week 8	*P* value versus placebo	Step 3 (n = 943) MezzoTinA-asthma Week 24	*P* value versus placebo	Step 4 (n = 866)† MezzoTinA-asthma and PrimoTinA-asthma* Week 24	*P* value versus placebo	Step 5 (n = 74) PrimoTinA-asthma Week 24	*P* value versus placebo
Absolute changes in $FEV_{1(0–3h)}$ peak, mL, mean (± SE)								
Tiotropium 5 µg	248 (19)	< 0.0001	244 (17)	< 0.0001	341 (25)	< 0.0001	449 (61)	0.0432
Tiotropium 2.5 µg	268 (19)	< 0.0001	292 (17)	< 0.0001	410 (65)	0.0152	NA	
Placebo	113 (19)		57 (17)		230 (25)		285 (52)	
Absolute changes in FEV_1 trough, mL, mean (± SE)								
Tiotropium 5 µg	135 (20)	< 0.0001	112 (19)	< 0.0001	170 (23)	< 0.0001	183 (56)	0.0881
Tiotropium 2.5 µg	139 (20)	< 0.0001	160 (19)	< 0.0001	244 (60)	0.0163	NA	
Placebo	23 (20)		−20 (19)		79 (23)		56 (48)	

*Data pooled for the purpose of this analysis. †Patient numbers for trough FEV_1 were 865 for Step 4. Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 s; $FEV_{1(0–3h)}$, forced expiratory volume in 1 s within 3 h post-dose; GINA, Global Initiative for Asthma; NA, not assessed; SE, standard error.

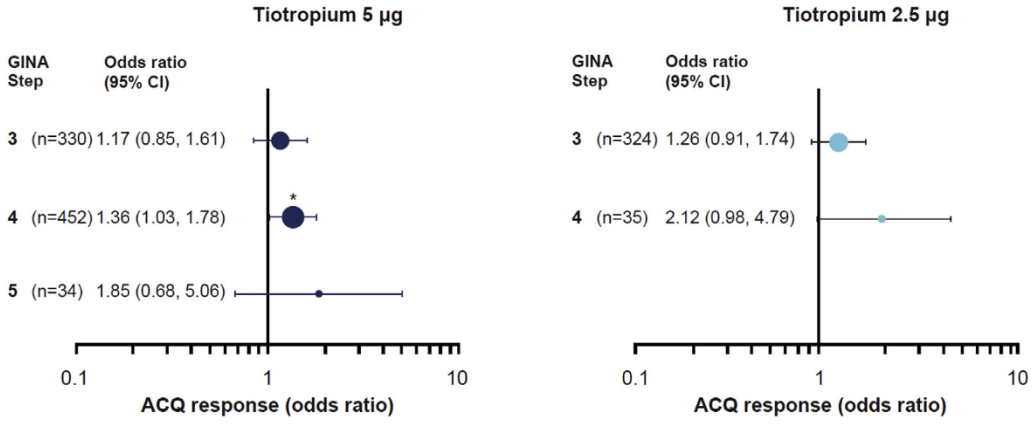

Fig. 3. Odds ratio for ACQ response for tiotropium Respimat versus placebo across GINA Steps. *$P < 0.05$; all vs placebo. Abbreviations: ACQ, Asthma Control Questionnaire; CI, confidence interval; GINA, Global Initiative for Asthma. ACQ was not measured at a common visit for GraziaTinA-asthma and MezzoTinA-asthma (i.e. the trials that included Step 2 patients); therefore, Step 2 asthma control data have not been pooled or analyzed here. Error bars represent 95% confidence interval values. N numbers describe patients treated with tiotropium Respimat. Symbol sizes approximate patient numbers using a 7-point scale ranging from 1 to 75 to 451–525 patients.

GraziaTinA-asthma [15,17,19], these improvements in lung function and asthma control were also observed in patients who had not necessarily experienced asthma exacerbations recently.

It is noteworthy that there was a greater placebo response in peak $FEV_{1(0–3h)}$ and trough FEV_1 in patients at Steps 4 and 5 compared with at Steps 2 and 3. The response in patients with more severe disease may be due to improved adherence to their medication regimen, as often occurs during participation in a clinical trial, as well as an increased probability of improvement given the higher disease severity. A large online survey of patients with asthma in Europe showed that over half of patients did not use their inhaler medication every day as prescribed [4].

While improvements in lung function were found at GINA Steps 2–5, these results do not follow a dose-response relationship. However, the numerically larger response observed with the 2.5 µg dose of tiotropium Respimat compared with 5 µg is unlikely to be clinically meaningful and may reflect the biologic variability of responses commonly observed in asthma patients. This observation is consistent with the results from the original Phase III GraziaTinA-asthma trial [19] and the MezzoTinA-asthma replicate trials [15], in which numerically higher values for the primary endpoint – peak $FEV_{1(0–3h)}$ response – were observed with the 2.5 µg dose of tiotropium Respimat compared with the 5 µg dose. Of note, these studies were not powered to demonstrate statistical differences between the two doses [15,19]. Tiotropium 2.5 µg is the approved dose in the US for asthma patients aged 6 years and older [9,22]. Overall, across this large-scale clinical trial program, both doses of add-on tiotropium (2.5 µg and 5 µg) were shown to be well tolerated and efficacious in patients with mild-to-moderate and severe asthma [7].

Despite the number of available asthma treatments, there remains an unmet need in achieving control in patients at all levels of disease severity [1–4]. Towards this goal, there is interest in understanding how tiotropium Respimat can be used in patients across different asthma severities. While tiotropium Respimat is primarily used to improve lung function and asthma control as an add-on to ICS/LABA therapy, there may also be further instances for its use, such as where other asthma treatments are not well tolerated, pose a higher risk of AEs, or are ineffective [8]. For example, tiotropium Respimat may be an alternative treatment to LABAs in particular clinical situations in patients at GINA Steps 2 and 3, such as in patients experiencing common LABA side effects such as tremor or palpitation [23], or in those who have an inadequate response or develop a tolerance to LABAs [24]. The independent trial “Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid” (TALC) showed that there were substantial numbers of GINA Step 3 patients with asthma that had improved lung function and asthma control as a response to either a LABA or tiotropium, but not to both [25,26]. This differential response may be reflective of examining mean group responses in clinical trials rather than individual responses to a specific therapy. Potentially, this suggests different underlying mechanisms of disease that require alternative treatment strategies [25].

Because of the heterogeneous nature of asthma, it is important that treatments are broadly effective or targeted at the correct patient population. Tiotropium Respimat has a different mode of action to other bronchodilator therapies and has demonstrated effectiveness independent of patient phenotype in different clinical trials [27]. In patients with severe asthma, exploratory analyses have shown that tiotropium Respimat is suitable in a range of patient phenotypes with heterogeneity in baseline characteristics that include age, body mass index, disease duration, age at asthma onset, degree of airway obstruction, smoking status (never smoked and ex-smokers), and allergic status [27]. The GINA strategy recommends the use of tiotropium by mist inhaler as add-on therapy for adult and adolescent patients at Steps 4 and 5 [5]. Indeed, the Respimat Soft Mist Inhaler™ device was used successfully by patients with severe asthma and persistent airflow obstruction, despite the use of ICS and LABAs [17]. Furthermore, given that LABAs are more effective in the distal airways, and anticholinergic agents, such as tiotropium, are more effective in the proximal airways, inhaled treatment with both classes of drugs exploits the full bronchodilatory potential in the entire bronchial tree [28]. As tiotropium is an effective treatment in more severe asthma (Step 5 patients), then in most cases it should be considered as an add-on treatment before extensive phenotyping and escalation to more costly targeted biologic therapies [29].

Our analysis also suggests the potential to extend the use of tiotropium to adult asthma patients classified as GINA Step 2 and 3. This would provide the advantage of adding tiotropium, delivered by means of the optimized Respimat device, to the patient's ICS regimen, rather than stepping up therapy with a conventional ICS/LABA combination inhaler. Indeed, in the independent National Institutes of Health (NIH) National Heart, Lung and Blood Institute (NHLBI)-sponsored Blacks and Exacerbations on LABA vs. Tiotropium (BELT) study, looking at use of LABAs and tiotropium in the African-American population, for both Step 3 and 4 patients, tiotropium was as effective as a LABA when added to ICS in terms of the primary outcome (time to first exacerbation) or other endpoints (lung function, ACQ) [30]. In addition, it was shown that add-on tiotropium was superior to a doubling of ICS dose with respect to improved lung function, reduced symptoms, and improved control in patients with symptomatic asthma at Step 3 [26]. It is the authors' opinion that similarly, and irrespective of GINA step, tiotropium can easily be added on to treatment strategies such as ICS/formoterol maintenance and reliever therapy.

The implications from our study are somewhat limited by the *post hoc* nature of the analysis, the number of clinical endpoints examined, and the small number of patients in the Step 5 subgroup. The original

studies ranged between 12 and 48 weeks in duration. Therefore, due to the shorter duration of some of the trials, and the low frequency of exacerbations in the lower GINA steps, exacerbations were not analyzed here. Exacerbations are an important clinical endpoint in asthma; indeed, the effect of tiotropium in reducing asthma exacerbations and episodes of poor asthma control compared with placebo have been previously demonstrated [14]. Additionally, the ACQ-7 clinical endpoint analyzed here combines patient-reported symptom scores with reliever use and pre-bronchodilator FEV_1 [5]. Hence, we were not able to show an impact on asthma control independent of lung function. As such, analysis of ACQ-5 or ACQ-6 may be preferable in future studies.

The current analyses do suggest that tiotropium Respimat is an effective add-on therapy in patients already at Steps 2–3. The results of this analysis add to the extensive data that support the use of add-on tiotropium across a broader range of asthma severity.

5. Conclusions

Addition of tiotropium Respimat 5 μg and 2.5 μg to maintenance therapy in adult patients with symptomatic asthma produces improvements in lung function across all GINA steps; further analysis of asthma control involving larger numbers of patients is warranted.

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Declaration of competing interest

RB has received grants and personal fees from Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Roche, and personal fees from AstraZeneca, Chiesi, and Teva. JMF reports being a member of advisory boards for AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi-Regeneron, Circassia, and Teva; has been paid honoraria for lecturing at symposia organized by AstraZeneca, Boehringer Ingelheim, Novartis, and Merck, and has also undertaken clinical trials through his employer, the University of British Columbia, for these companies and GlaxoSmithKline. EOM reports consultancies for ALK, Allergan, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Glenmark, Gossamer Bio, Johnson & Johnson, Merck, Mylan, Regeneron, Sanofi, and Teva, and has also attended speaker's bureaus for ALK, GlaxoSmithKline, Glenmark, Merck, Mylan, and Teva. ADLH and RS are employees of Boehringer Ingelheim. HAMK reports that his institution has received a fee per patient for recruitment, as well as consultancy fees for advisory boards from Boehringer Ingelheim during the conduct of the current study. Additionally, his institution has received grants, as well as consultancy fees and fees per patient recruited for trials, from GlaxoSmithKline, Novartis, AstraZeneca, and Boehringer Ingelheim outside of the submitted work. ERB has performed clinical trials administered by his former employer, the Wake Forest School of Medicine and currently the University of Arizona, and has served as a paid consultant for AstraZeneca, Boehringer Ingelheim, GSK, MedImmune, Novartis, Regeneron, and Sanofi-Genzyme.

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Appendix A. Supplementary data

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